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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,833	01/11/2002	Jim Wells	SUNESIS.2DV1C1	3663

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
File Copy	10/043,833	WELLS ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-62* is/are pending in the application.

4a) Of the above claim(s) *42,43,54,55 and 57-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,41,44-53 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Please note: The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Group Art Unit 1639**.

Status of the Application

1. Receipt is acknowledged of a Response to Restriction Requirement, which was dated on December 12, 2002 (Paper No. 10).

Priority Claims

2. The priority filing date of June 26, 1998 is acknowledged for applications 09/981,547 (CON) and 09/105,372 (DIV).

Status of the Claims

3. Claims 40-62 are pending in the present application in accordance with applicants transmittal sheet and Preliminary Amendments.

4. Applicant's response to the Restriction and/or Election of Species requirements in Paper No. 10 is acknowledged (Applicant elected Group I, claims 40-56 with traverse) and claims 57-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., ***Response to Restriction and/or Election of Species***).

5. Claims 42-43 and 54-55 are also withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in Paper No. 14 (see below i.e., ***Response to Restriction and/or Election of Species***).

6. Therefore, claims 40-41, 44-53 and 56 are examined on the merits in this action.

Response to Restriction and Election of Species

7. Applicant's election of Group I (claims 40-56) with traverse in Paper No. 10 is acknowledged.

8. The traversal is on the ground(s) that "claims 40-56, and 57-62 show a significant degree of overlap, and all relate to screening methods in order to identify small molecule ligands with binding affinity for a target. Accordingly, examining the claims of Groups I and II would not place an undue burden on the Examiner, rather would facilitate the prosecution of the application" (see Paper No. 10, page 2).

9. These arguments were fully considered but were not found persuasive. Groups I and II represent separate and patentably distinct methods for the reasons of record. (see Paper No. 9, paragraph 3, "In this case, the method of Group I employs a target "protein"-ligand whereas the method of Group II employs a target "biological molecule", which would not necessarily include a "protein" conjugate. For example, the "target biological molecule" could include a "nucleic

acid" or "polysaccharides", which would lead to different searches in different classifications e.g., class 435, DIG 18 for the "nucleic acid" or class 435, DIG 17 for the "polysaccharide" as opposed to class 435 DIG 15 for the "proteins" in Group I").

10. Therefore, the groups that describe these methods (i.e., Groups I-II) have different issues regarding patentability and enablement, and represent patentably distinct subject matter, which merits separate and burdensome searches. The different methods would require completely different searches in both the patent and non-patent databases, and there is no expectation that the searches would be coextensive i.e., the Groups can be separately classified (see above). Art anticipating or rendering obvious each of the above-identified groups respectively would not necessarily anticipate or render obvious another group, because they are drawn to different inventions that have different distinguishing features and/or characteristics. Each group will support separate patents.

11. Applicant's election of species in Paper No. 10 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a)).

12. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

13. The information disclosure statement filed February 16, 2002, fails, in part, to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because two publications cited therein, numbered 17 and 21, lack publication dates, a necessary element for consideration. While the other patent and other publications cited therein, and supplied, therewith, have been considered as to the merits, these three publications have not. Applicant is advised that the date of any re-submission of these citations contained in this information disclosure statement or the submission of the missing element – their publication dates – will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPE § 609 C(1).

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 40-41, 44-53 and 56 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description"

Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claim 40 outlines method steps for screening a library of "small organic compounds" using a "target protein-ligand conjugate" with "first" and "second" reactive functionalities, wherein no structural features or identifying characteristics are given for the "small organic molecules", "target protein-ligand conjugate" or the "first" and "second" reactive functionalities. The scope of this claim includes an infinite number of methods for identifying an infinite number of small organic compounds using an infinite number of target proteins and an infinite number of ligands. Furthermore, the specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the "target protein", "ligand", "small organic compounds", or the "first" and "second" reactive functionalities contained therein. Consequently, it is not possible to determine *a priori* which "proteins", "ligands", "small organic molecules", "first and second functionalities" would be encompassed by the present claims because there is no commonality that can link together ***all*** of these unknown variables i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* what "proteins", "ligands", "small organic molecules" and "functionalities" should be included in this genus from the few working examples provided by applicants.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, ***not general***, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant,

simply reciting a "laundry list" of potential biological target molecules, chemically reactive groups and target proteins (e.g., see specification, page 8, last paragraph, wherein target protein may be "enzymes, such as proteases and thymidylate synthease, steroid receptors, nuclear proteins, allosteric enzyme inhibitors, clotting factors ... etc.") is insufficient to teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicants were not in possession of the claimed genus.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 40-41, 44-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**).

For **claim 40**, Pitner et al (see entire document) teaches a method for modifying antibodies, which anticipates claim 40. For example, Pitner et al discloses [a] screening a library of small organic compounds e.g., antibody antigens (see Pitner et al, figure 1; see also figure 6 showing PC and PC-TP antigens; see also Figure 7 showing PC and PC-MAL antigens; see also Figure 11 showing GlcNAc and GlcNAc-TP antigens; see also

Figure 12 showing GlcNAc and ClcNAc-MAL antigens), [b] with a target protein ligand conjugate formed by the covalent bonding of a biological target molecule comprising a first reactive functionality with a compound that comprises (1) a second reactive functionality and (2) a chemically reactive group, wherein the second reactive functionality of the compound reacts with the first reactive functionality of the biological target molecule to form a first covalent bond such that the protein-ligand conjugate contains a free chemically reactive group (see Pitner et al, figure 1 wherein said target biological molecule is the McPC603 antibody, the first reactive functionality is the -NH2 group on the antibody, the second reactive functionality is the ketone on the affinity label that reacts with the -NH2 group to form a covalent bond, the chemically reactive group is the -S-S- that is set "free" in DTT to become an -SH), [c] wherein at least one member of the library forms a second covalent with the target protein-ligand conjugate (see Pitner et al, figure 5 wherein the target-protein ligand conjugate is McPC603-SH and the "at least one member of the library" is PC-TP; see also figure 6 wherein the "at least one member of the library" is PC-MAL; see also figures 11 and 12, using modified st9 and GlcNAc antigens), [d] identifying a small organic compound that binds covalently to the chemically reactive group thereby forming a complex (see figures 5-6 and 11-12 showing antigen/antibody binding curved e.g., "identification" of which antigens bind and by how much).

For **claim 41**, Pitner et al discloses the second covalent bond is a disulfide bond (see Pitner et al, figure 1, see also column 6, paragraph 2).

For **claim 44**, Pitner et al discloses a free thiol (see Pitner et al, figure 1, see also column 6, paragraph 2).

For **claim 45**, Pitner et al discloses library members with thiols and disulfides (see Pitner et al, figure 1, see also column 6, paragraph 2).

For **claim 46**, Pitner et al discloses all library members with amides (see Pitner et al, figure-8 showing all GlcNAc library members with NHAc groups).

16. Claims 40-41, 44-46 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Janda et al (Janda, K. D.; Lo, C. –H. L.; Li, T.; Barbas, C. F.; Wirsching, P.; Lerner, R. A. "Direct selection for a catalytic mechanism from combinatorial antibody libraries" *PNAS* **March 1994**, *91*, 2532-2536).

For **claim 40**, Janda et al (see entire document) teaches a method for screening a combinatorial antibody library for enzymatic activity, which anticipates claim 40. For example, Janda et al discloses [a] screening a library of small organic compounds e.g., catalytic antibody substrates (see Janda et al, figure 1, compounds 1-6, see also page 2533, column 1, paragraph 2 for generation of antibody library), [b] with a target protein ligand conjugate formed by the covalent bonding of a biological target molecule comprising a first reactive functionality with a compound that comprises (1) a second reactive functionality and (2) a chemically reactive group, wherein the second reactive functionality of the compound reacts with the first reactive functionality of the biological target molecule to form a first covalent bond such that the protein-ligand conjugate

contains a free chemically reactive group (see Janda et al, figures 1-2 showing reaction of compound 1, i.e. the ligand, with BSA, i.e. the target protein, wherein compound 1 contains "a second reactive functionality", i.e. the N-hydroxysuccinimide ester, that reacts with a "first reactive functionality" on the target protein, i.e. an amino group, to form a covalent bond leaving a disulfide bond, i.e., a chemically reactive group, for covalent attachment to the antibody [c] wherein at least one member of the library forms a second covalent with the target protein-ligand conjugate (see Janda et al, figure 2; see also page 2533, column 2, last two paragraphs), [d] identifying a small organic compound that binds covalently to the chemically reactive group thereby forming a complex (see Janda et al, page 2533, last paragraph; see also Materials and Methods section).

For **claim 41**, Janda et al discloses the second covalent bond is a disulfide bond (see Janda et al, figure 2 showing formation of disulfide).

For **claim 44**, Janda et al discloses a free thiol (see Janda et al, figure 2).

For **claim 45**, Janda et al discloses library members with thiols and disulfides (see Janda et al, figures 1-2).

For **claim 46**, Janda et al discloses all library members with amides (see Janda et al, figure 2).

For **claim 56**, Janda et al discloses enzymes i.e., catalytic antibodies (see Janda et al, abstract).

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 40-41, 44-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is November 22, 1994) and Loo, J. A. (Loo, J. A. "Studying Noncovalent Protein Complexes by Electrospray Ionization Mass Spectrometry" *Mass Spectrometry Reviews*, **1997**, *16*, 1-23).

For **claims 40-41 and 44-46**, Pitner et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 40-41 and 44-46 and, consequently, also renders obvious claims 40-41 and 44-46.

The prior art teachings of Pitner et al differ from the claimed invention as follows:

For **claims 47-48**, Pitner et al is deficient in that it does not specifically teach the use of "mass spectrometry" for the identifying step. Pitner et al used UV/Vis for detection.

For **claim 49**, Pitner et al is deficient in that it does not specifically teach the use of fragmentation prior to subjecting it to mass spectrometry.

However, Loo teaches the following limitations that Pitner et al lacks:

For **claims 47-48**, Loo teaches the use of mass spectroscopy for the "identification of novel protein-ligand interactions" including "antibody-antigen" conjugates (see Loo, entire document, especially page 14, section VI, paragraph 2, see also page 2, paragraph 1; see also abstract; see especially Table 1 showing many examples of protein-ligand interactions being studied by mass spectroscopy).

For **claim 49**, Loo et al teaches fragmentation via tandem mass spectrometry (see Loo, page 4, column 1, paragraph 3).

It would have been obvious to one skilled in the art at the time the invention was made to "identify" antibody/antigen interactions using the method steps as taught by Pitner et al in conjunction with the mass spectrometer techniques for the "identification of novel protein-ligand interactions" as taught by Loo because Loo explicitly states that the mass spectrometry can be applied to a broad range of protein-ligand interactions including "antibody-antigen" complexes (see Loo, page 2, paragraph 1), which would encompass the "antibody-antigen" complexes of Pitner et al. Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as

taught by Loo with the antibody-antigen conjugates as taught by Pitner et al because Loo explicitly states that mass spectroscopy offers many advantages including speed, sensitivity, stoichiometry and mass accuracy (see Loo, abstract, see also page 4, column 1) for analyzing the protein/ligand interactions and their binding affinities.

20. Claims 40-41, 44-48 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**) and Ganem et al (Ganem, B.; Li, Y. T.; Henion, J. D. "Detection of noncovalent receptor-ligand complexes by mass spectrometry" *Journal of the American Chemical Society* **1991**, 113(16), 6294-6).

For **claims 40-41 and 44-46**, Pitner et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 40-41 and 44-46 and, consequently, also renders obvious claims 40-41 and 44-46.

The prior art teachings of Pitner et al differ from the claimed invention as follows:

For **claims 47-48**, Pitner et al is deficient in that it does not specifically teach the use of "mass spectrometry" for the identifying step. Pitner et al used UV/Vis for detection.

However, Ganem et al teaches the following limitations that Pitner et al lacks:

For **claim 47-48**, Ganem et al (see entire document) teaches the use of mass spectroscopy for "identifying enzyme-substrate, receptor-ligand ... complexes" (see Ganem et al, page 6294, paragraph 1; see also, page 6295, second column, last

paragraph). Furthermore, Ganem et al teaches that the ligand can be "identified" using mass spectrometry without purification (see Ganem et al, page 6296, "This result indicates that noncovalently bound species can be detected directly in a complex mixture without chromatographic separation"; see also figure 3, peak 1803.1 showing FKBP/FK506 complex).

It would have been obvious to one skilled in the art at the time the invention was made to "screen a library of small organic compounds" as taught by Pitner et al in conjunction with the mass spectrometer techniques as taught by Ganem et al because Ganem et al explicitly states that the mass spectrometry "can be applied to problems of biological interest [including] ... proteins" and that the methods are good for "detecting and identifying enzyme-substrate, receptor-ligand [complexes]", (see Ganem et al, page 6294, paragraph 1) (see also page 6296 wherein Ganem specifically refers to "antibody-antigen" complexes as well), which would encompass the "antibody-antigen" complexes of Pitner et al. Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Ganem et al with the ligand-receptors as taught by the teachings of Pitner et al because Ganem et al explicitly states that the "ion-spray MS can be performed in water without cosolvent, which is ideal for most biological systems. Multiple charging produces a family of molecular ions and dramatically reduces the mass-to-charge ratio so that even quadrupole mass spectrometers having a typical range of 1000-2000 daltons (DA) can determine high MW species with unit mass resolution" (see Ganem et al, page 6294, second paragraph) (see also Ganem et al, page 6296, last paragraph).

21. Claims 40-41, 44-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**) and Przybylski et al (Przybylski, M.; Glocker, M. O. "Electrospray Mass Spectrometry of Biomacromolecular Complexes with Noncovalent Interactions-New Analytical Perspecties for Supramolecular Chemistry and Molecular Recognition Processes" Angew. Chem. Int. Ed. Engl. **1996**, 35, 806-826) and Wunsch et al (Wunsch, E.; Spangenberg, R., in Peptides, 1969, E. Schoffone, Ed., North Holland, Amsterdam, P. 1971. Please note the original reference will be provided when it becomes available; an excerpt from Greene, T. W. et al is provided which references the Wunsch article i.e., Greene, T. W.; Wuts, P. G. M. in Protective Groups in Organic Synthesis, 1999, John Wiley & Sons, Inc., New York, page 487) (This reference is provided solely to show the state of the art with regard to disulfide bond cleavage).

For **claims 40-41 and 44-46**, Pitner et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 40-41 and 44-46 and, consequently, also renders obvious claims 40-41 and 44-46.

The prior art teachings of Pitner et al differ from the claimed invention as follows:

For **claims 47-48**, Pitner et al is deficient in that it does not specifically teach the use of "mass spectrometry" for the identifying step. Pitner et al used UV/Vis for detection.

For **claim 49**, Pitner et al is deficient in that it does not specifically teach the use of fragmentation prior to subjecting it to mass spectrometry.

For **claims 50-52**, Pitner et al is deficient in that it does not specifically teach the use of liberating or releasing the small organic compound from the complex prior to subjecting it to mass spectrometry.

However, Przybylski et al teaches the following limitations that Pitner et al lacks:

For **claim 47-48**, Przybylski et al (see entire document) teaches the use of mass spectroscopy for "receptor-ligand interactions" including "antibody-antigen" interactions (see Przybylski et al, page 823, last paragraph; see also page 808, column 1, paragraph 1; see also abstract; see also page 812, section 2.3, paragraph 1). Furthermore, Przybylski et al teaches that the ligand can be "identified" using mass spectrometry without purification (see Przybylski et al, page 808, column 2, paragraph 2, "ESI-MS is applicable to relatively impure samples").

For **claim 49**, Przybylski et al teaches the use of fragmentation both by enzymatic techniques (i.e., fractionation by enzyme cleavage before detection) and by the use of mass spectrometry techniques e.g., tandem-ESI-MS upon collision induced dissociation (see Przybylski et al, figure 9; see also page 817, column 1, paragraph 2).

For **claims 50-52**, Przybylski et al teaches the use of DTT (see Figure 9, bottom spectrum). Furthermore, applicant's specification does not teach the criticality of using one particular agent and, as a result, any reducing agent would be immediately envisaged for this application including sodium borohydride and any other common reducing agents known in the art see Wunsch et al (Wunsch, E.; Spangenberg, R., in Peptides, 1969, E.

Schoffone, Ed., North Holland, Amsterdam, P. 1971. Please note the original reference will be provided when it becomes available; an excerpt from Greene, T. W. et al is provided which references the Wunsch article i.e., Greene, T. W.; Wuts, P. G. M. in Protective Groups in Organic Synthesis, 1999, John Wiley & Sons, Inc., New York, page 487) (This reference is provided solely to show the state of the art with regard to disulfide bond cleavage showing cleavage of s-*t*-butyl disulfide with sodium borohydride).

It would have been obvious to one skilled in the art at the time the invention was made to "screen a library of small organic compounds" as taught by Pitner et al in conjunction with the mass spectrometer techniques as taught by Przybylski et al because Przybylski et al explicitly states that the mass spectrometry can be applied to "antibody-antigen" complexes (see Przybylski et al, page), which would encompass the "antibody-antigen" complexes of Pitner et al and, consequently, the Przybylski et al reference would point one of ordinary skill to the Pitner et al reference. Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Przybylski et al with the ligand-receptors as taught by the teachings of Pitner et al because Przybylski et al explicitly states many advantage of mass spectroscopy for studying protein-ligand interactions including [a] "breakthrough" to macromolecules larger than 100 kDa, [b] high resolution, [c] usefulness in determining protein-ligand stoichiometries, [d] determinations of equilibrium constants, and [e] the fact that ESI-MS can be readily carried out with aqueous solutions at nearly physiological solution condition, thus enabling comparison with other methods of structure determination and NMR spectrscopy (see Przybylski et al, abstract; see also page 815, column 2, paragraph

1; see also page 816, column 2, paragraph 1; see also page 808, column 2, paragraph 1). A person of skill in the art would have reasonably expected to be successful because Przybylesk et al provides many examples of successful application of ESI-MS to protein-ligand conjugates including combinatorial screening (see entire document, especially page 823, last paragraph).

22. Claims 40-41, 44-52, 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janda et al (Janda, K. D.; Lo, C. –H. L.; Li, T.; Barbas, C. F.; Wirsching, P.; Lerner, R. A. "Direct selection for a catalytice mechanism from combinatorial antibody libraries" *PNAS* **March 1994**, *91*, 2532-2536) and Przybylski et al (Przybylski, M.; Glocker, M. O. "Electrospray Mass Spectrometry of Biomacromolecular Complexes with Noncovalent Interactions-New Analytical Perspecties for Supramolecular Chemistry and Molecular Recognition Processes" Angew. Chem. Int. Ed. Engl. **1996**, 35, 806-826) and Wunsch et al (Wunsch, E.; Spangenberg, R., in Peptides, 1969, E. Schoffone, Ed., North Holland, Amsterdam, P. 1971. Please note the original reference will be provided when it becomes available; an excerpt from Greene, T. W. et al is provided which references the Wunsch article i.e., Greene, T. W.; Wuts, P. G. M. in Protective Groups in Organic Synthesis, 1999, John Wiley & Sons, Inc., New York, page 487) (This reference is provided solely to show the state of the art with regard to disulfide bond cleavage).

For **claims 40-41 and 44-46**, Janda et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which

anticipates claims 40-41, 44-46, 56 and, consequently, also renders obvious claims 40-41, 44-46 and 56.

The prior art teachings of Janda et al differ from the claimed invention as follows:

For **claims 47-48**, Janda et al is deficient in that it does not specifically teach the use of "mass spectrometry" for the identifying step. Janda et al used UV/Vis for detection.

For **claim 49**, Janda et al is deficient in that it does not specifically teach the use of fragmentation prior to subjecting it to mass spectrometry.

For **claims 50-52**, Janda et al is deficient in that it does not specifically teach the use of liberating or releasing the small organic compound from the complex prior to subjecting it to mass spectrometry. Janda et al only teaches the use of liberating the small organic molecule without using mass spectrometry (see Figure 2, application of DTT; see also page 2534, column 1, paragraph 1 showing use of Elman's reagent).

However, Przybylski et al teaches the following limitations that Janda et al lacks:

For **claim 47-48**, Przybylski et al (see entire document) teaches the use of mass spectroscopy for "receptor-ligand interactions" including "antibody-antigen" interactions (see Przybylski et al, page 823, last paragraph; see also page 808, column 1, paragraph 1; see also abstract; see also page 812, section 2.3, paragraph 1). Furthermore, Przybylski et al teaches that the ligand can be "identified" using mass spectrometry with or without purification (see Przybylski et al, page 808, column 2, paragraph 2, "ESI-MS is applicable to relatively impure samples and multicomponent mixtures and is compatible with microanalytical separation techniques").

For **claim 49**, Przybylski et al teaches the use of fragmentation both by enzymatic techniques (i.e., fractionation by enzyme cleavage before detection) and by the use of mass spectrometry techniques e.g., tandem-ESI-MS upon collision induced dissociation (see Przybylski et al, figure 9; see also page 817, column 1, paragraph 2).

For **claims 50-52**, Przybylski et al teaches the use of DTT (see Figure 9, bottom spectrum). Furthermore, applicant's specification does not teach the criticality of using one particular agent and, as a result, any reducing agent would be immediately envisaged for this application including sodium borohydride and any other common reducing agents known in the art Wunsch et al (Wunsch, E.; Spangenberg, R., in Peptides, 1969, E. Schoffone, Ed., North Holland, Amsterdam, P. 1971. Please note the original reference will be provided when it becomes available; an excerpt from Greene, T. W. et al is provided which references the Wunsch article i.e., Greene, T. W.; Wuts, P. G. M. in Protective Groups in Organic Synthesis, 1999, John Wiley & Sons, Inc., New York, page 487) (This reference is provided solely to show the state of the art with regard to disulfide bond cleavage showing cleavage of s-*t*-butyl disulfide with sodium borohydride).

It would have been obvious to one skilled in the art at the time the invention was made to "screen a library" as taught by Janda et al in conjunction with the mass spectrometer techniques as taught by Przybylski et al because Przybylski et al explicitly states that the mass spectrometry can be applied to "antibody-antigen" complexes (see Przybylski et al, page), which would encompass the "antibody-antigen" complexes of Janda et al and, consequently, the Przybylski et al reference would point one of ordinary skill to the Janda et al reference. Furthermore, one of ordinary skill in the art would have

been motivated to use the mass spectrometers as taught by Przybylski et al with the ligand-receptors as taught by the teachings of Janda et al because Przybylski et al explicitly states many advantage of mass spectroscopy for studying protein-ligand interactions including [a] "breakthrough" to macromolecules larger than 100 kDa, [b] high resolution, [c] usefulness in determining protein-ligand stoichiometries, [d] determinations of equilibrium constants, and [e] the fact that ESI-MS can be readily carried out with aqueous solutions at nearly physiological solution condition, thus enabling comparison with other methods of structure determination and NMR spectrscopy (see Przybylski et al, abstract; see also page 815, column 2, paragraph 1; see also page 816, column 2, paragraph 1; see also page 808, column 2, paragraph 1). A person of skill in the art would have reasonably expected to be successful because Przybylesk et al provides many examples of successful application of ESI-MS to protein-ligand conjugates including combinatorial screening (see entire document, especially page 823, last paragraph).

23. Claims 40-41 and 44-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**) and Przybylski et al (Przybylski, M.; Glocker, M. O. "Electrospray Mass Spectrometry of Biomacromolecular Complexes with Noncovalent Interactions-New Analytical Perspecties for Supramolecular Chemistry and Molecular Recognition Processes" Angew. Chem. Int. Ed. Engl. **1996**, 35, 806-826) and Crooke et al (US Patent No. 6,428,956) (Filing Date is **May 12, 1998**).

For **claims 40-41 and 44-52**, the combined teachings of Pitner et al and Przybylski et al teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 40-41 and 44-52 and 56.

The combined prior art teachings of Pitner et al and Przybylski et al differ from the claimed invention as follows:

For **claim 53**, the combined teachings of Pitner et al Pryzybylski et al are deficient in that it does not teach the use of labeled probes.

However, Crooke et al teaches the following limitations that the combined teachings of Pitner et al and Przybylski et al lack:

For **claim 53**, Crooke et al (see entire document) teaches the use mass tags in combinatorial screening techniques (see Crooke et al, column 7, paragraph 2), which anticipates the "labled probes" because the masked tag acts to label the compounds via a mass label.

It would have been obvious to one skilled in the art at the time the invention was made to "screen a library" as taught by Pitner et al in conjunction with the mass spectrometer techniques as taught by Przybylski et al and in further conjunction with the "mass tags" (i.e., labeled probes) as taught by Crooke et al because Crooke et al explicitly states that the mass tags can be used for receptor-ligand complexes (see Crooke et al, abstract), which would encompass the "antibody-antigen" complexes (Crooke et al also sites various antibody-antigen papers as examples). One would have been motivated to use the "mass labels" of Crooke et al because according to Crooke they are useful in

situations where "mass redundancy is a concern, especially if two or more targets are of similar ... mass" (see Crooke et al, column 7, second paragraph; see also claims e.g., 1, 4, 6, 7, 10, 11; see also column 23, line 29).

24. Claims 40-41, 44-53 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janda et al (Janda, K. D.; Lo, C. –H. L.; Li, T.; Barbas, C. F.; Wirsching, P.; Lerner, R. A. "Direct selection for a catalytice mechanism from combinatorial antibody libraries" *PNAS* **March 1994**, *91*, 2532-2536) and Przybylski et al (Przybylski, M.; Glocker, M. O. "Electrospray Mass Spectrometry of Biomacromolecular Complexes with Noncovalent Interactions-New Analytical Perspecties for Supramolecular Chemistry and Molecular Recognition Processes" Angew. Chem. Int. Ed. Engl. **1996**, 35, 806-826) and Crooke et al (US Patent No. 6,428,956) (Filing Date is **May 12, 1998**).

For **claims 40-41, 44-52 and 56**, the combined teachings of Janda et al and Przybylski et al teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 40-41 and 44-52 and 56.

The combined prior art teachings of Janda et al and Przybylski et al differ from the claimed invention as follows:

For **claim 53**, the combined teachings of Janda et al Pryzybylski et al are deficient in that it does not teach the use of labeled probes.

However, Crooke et al teaches the following limitations that the combined teachings of Janda et al and Przybylski et al lack:

For **claim 53**, Crooke et al (see entire document) teaches the use mass tags in combinatorial screening techniques (see Crooke et al, column 7, paragraph 2), which anticipates the "labled probes" because the masked tag acts to label the compounds via a mass label.

It would have been obvious to one skilled in the art at the time the invention was made to "screen a library" as taught by Janda et al in conjunction with the mass spectrometer techniques as taught by Przybylski et al and in further conjunction with the "mass tags" (i.e., labeled probes) as taught by Crooke et al because Crooke et al explicitly states that the mass tags can be used for receptor-ligand complexes (see Crooke et al, abstract), which would encompass the "antibody-antigen" complexes (Crooke et al also sites various antibody-antigen papers as examples). One would have been motivated to use the "mass labels" of Crooke et al because according to Crooke they are useful in situations where "mass redundancy is a concern, especially if two or more targets are of similar ... mass" (see Crooke et al, column 7, second paragraph; see also claims e.g., 1, 4, 6, 7, 10, 11; see also column 23, line 29).

Double Patenting

25. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

26. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

27. Claims 40-41, 44-53 and 56 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent Application Publication 2002/0022233 A1 (see especially claims 12-31 of '233). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the referenced patent are drawn essentially to same method of screening a library and, as a result, the inventions overlap in scope. For example, both references recite [a] method steps for screening a library of small organic compounds (compare claim 14 of '233 to claim 40 of the present application), [b] with a target protein-ligand conjugate formed by the covalent bonding of a biological target molecule comprising a first reactive functionality with a compound that comprises a second reactive functionality and a chemically reactive group (compare claims 13,

14 (b) and 19 of '233 to claim 40 of the present application), [c] wherein the second reactive functionality of he compound reacts with the first reactive functionality of the biological target molecule to form a first covalent bond such that the protein-ligand conjugate contains a free chemically reactive group under conditions wherein at least one member of the library forms a second covalent (compare claim 14 (c) and 19 of '233 to claim 40 of the present application), and [d] identifying a small organic compound that binds covalently to the chemically reactive group thereby forming a covalent complex (compare claims 14 (d) of '233 to claim 40 (b) of the present application). Accordingly it is deemed that the inventions claimed herein and that of the patent are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

28. Claims 40-41, 44-53 and 56 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent Application Publication 2002/0081621 A1 (see especially claims 13-31 of '621). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the referenced patent are drawn essentially to same method of screening a library and, as a result, the inventions overlap in scope. For example, both references recite [a] method steps for screening a library of small organic compounds (compare claim 14 of '621 to claim 40 of the present application), [b] with a target protein-ligand conjugate formed by the covalent bonding of a biological target molecule comprising a first reactive functionality with a compound that comprises a second reactive functionality and a chemically reactive group (compare claims 13,

14 (b) and 19 of '621 to claim 40 of the present application), [c] wherein the second reactive functionality of he compound reacts with the first reactive functionality of the biological target molecule to form a first covalent bond such that the protein-ligand conjugate contains a free chemically reactive group under conditions wherein at least one member of the library forms a second covalent bond (compare claim 14 (c) and 19 of '621 to claim 40 of the present application), and [d] identifying a small organic compound that binds covalently to the chemically reactive group thereby forming a covalent complex (compare claims 14 (d) of '621 to claim 40 (b) of the present application). Accordingly it is deemed that the inventions claimed herein and that of the patent are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Status of Claims/Conclusion

29. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

32. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.
February 18, 2003

BENNETT CELSA
PRIMARY EXAMINER